U.S. FOOD & DRUG ADMINISTRATION

FDA Clinical Investigator Training Course

Real-World Evidence

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Disclaimer

- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**

- **No conflicts of interest exist related to this presentation**

Outline of Presentation

- Describe FDA's Real-World Evidence (RWE) Program
- Discuss terms for study design commonly used in drug development
- Highlight intersection of scientific and legal/regulatory issues related to study design in the RWE era
- Provide examples of "real-world evidence" in drug approvals

21st Century Cures Act (2016)

- **FDA *established* a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework *issued* in December 2018:**
  - **Describe sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry *issued* in September and October 2021**
- **Standard for substantial evidence remains unchanged; *commitments met* for Prescription Drug User Fee Act (PDUFA) VI**

Background: 'Real-World' Definitions (FDA 2018)

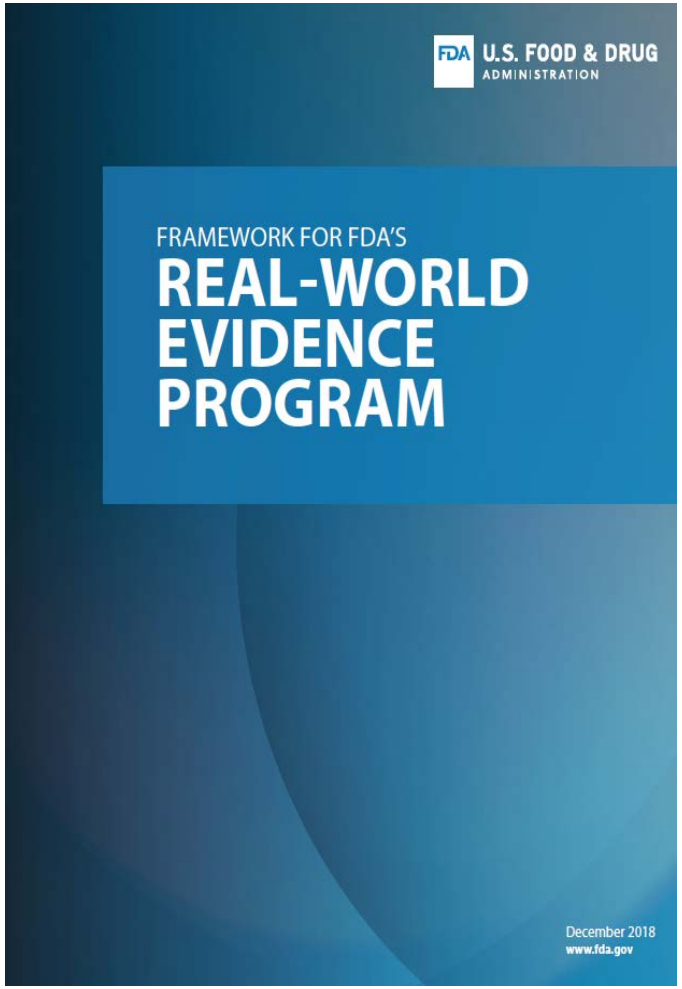
Real World Data (RWD) are data relating to patient health status and/or delivery of health care routinely collected from a variety of sources

- electronic health records (EHRs)
- medical claims data
- product and disease registries
- patient-generated data, including from in-home settings
- other sources that can inform on health status, such as "wearable" devices

Real World Evidence (RWE) is clinical evidence regarding the usage and potential benefits/risks of a medical product derived from analysis of RWD

Generated using different study designs, including but not limited to randomized trials (e.g., pragmatic clinical trials), externally controlled trials, or observational studies

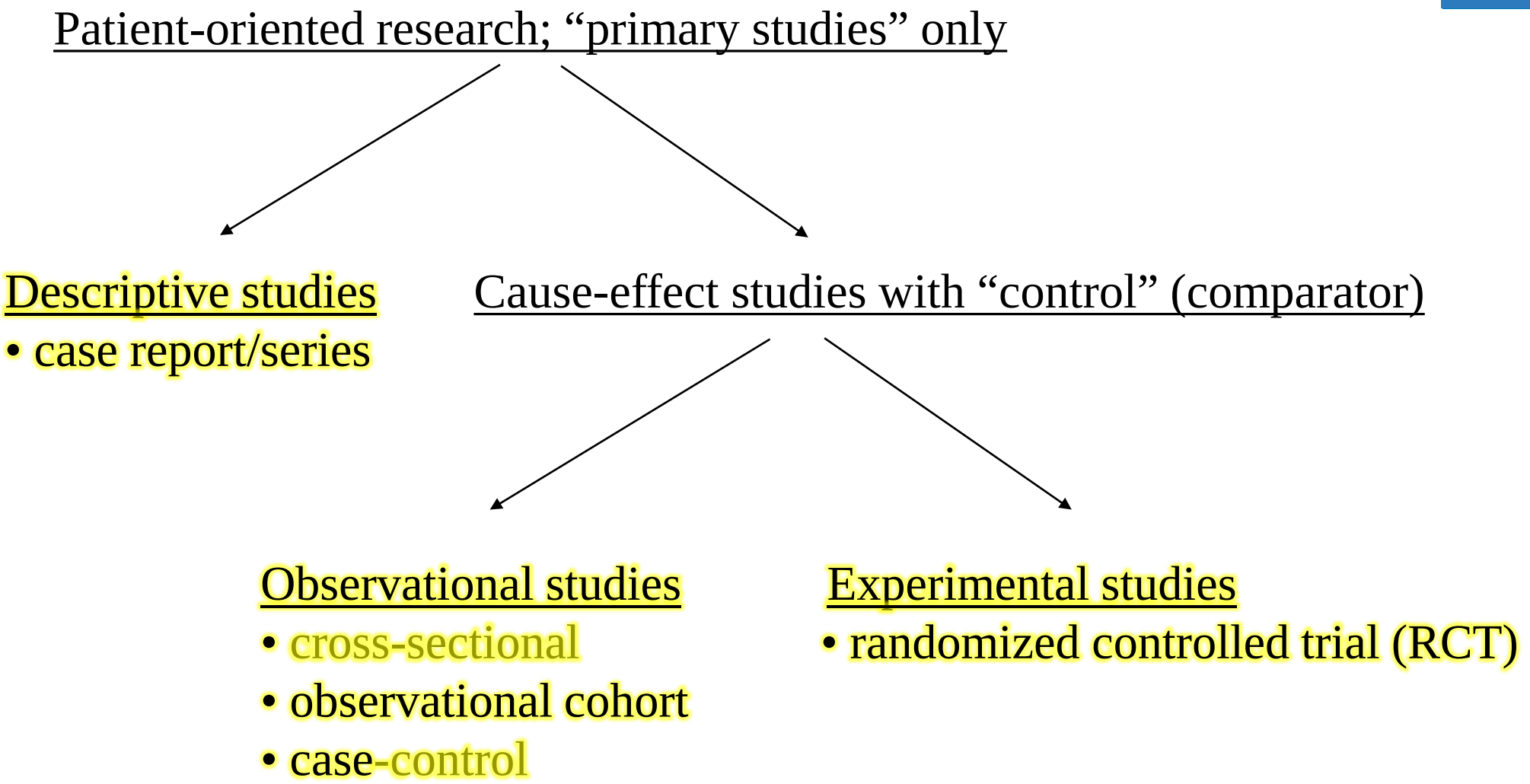
FDA RWE Framework (2018)



- **Applies only to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)**
- **Multifaceted program to implement RWE:**
  - **internal processes**
  - **external stakeholder engagement**
  - **guidance development**
  - **demonstration projects**

https://www.fda.gov/media/120060/download

Traditional Terms for Study Design



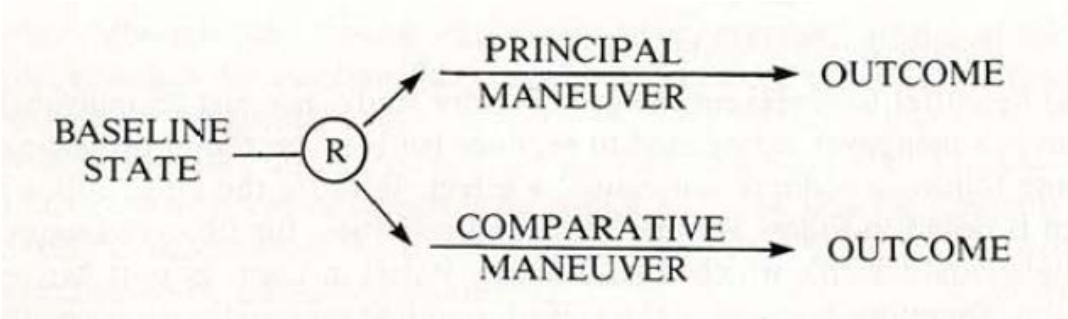
Concato *J Law and Policy* 2004;XII:489-507

Cause-Effect (Drug-Outcome) Associations

Schematic of drug-outcome associations for safety & effectiveness:

- **Patients at baseline → receipt of drug or comparator → evaluation of outcome**

Example of randomized trial:



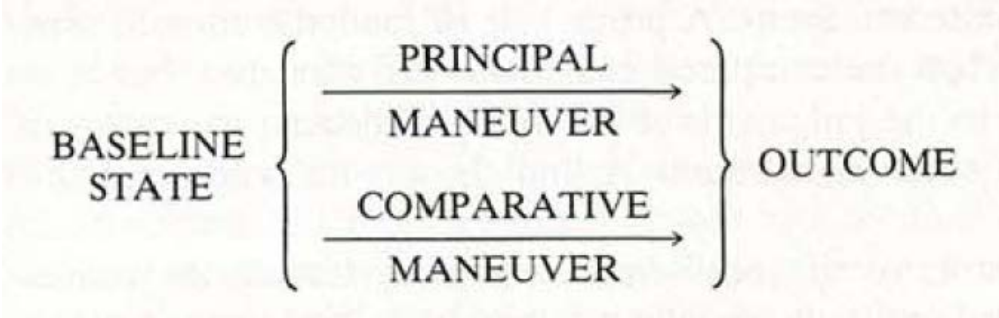
- **Is the validity of the comparison affected by source(s) of methodologic bias?**
  - randomization promotes balance at baseline to help minimize bias—and for decades has been the preferred method for evaluating drug safety/efficacy

Drug-Outcome Associations (cont'd)

Schematic of drug-outcome associations for safety & effectiveness:

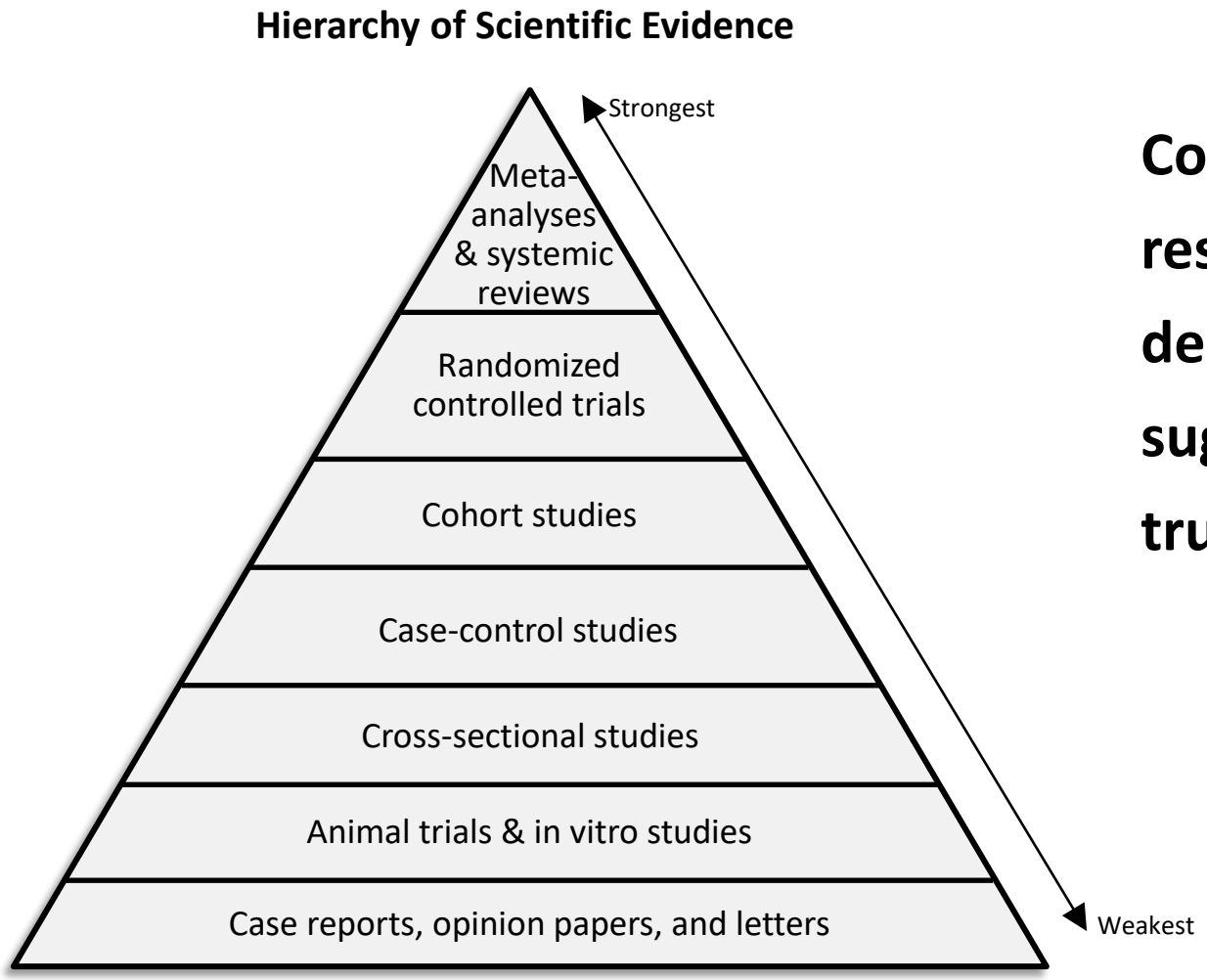
- **Patients at baseline → receipt of drug or comparator → evaluation of outcome**

Example without randomization:



- **Is the validity of the comparison affected by source(s) of methodologic bias?**
  - **"observational" studies need to address baseline imbalances to minimize bias (e.g., account for drug of interest given preferentially to patients more likely to have better or worse outcomes)**

Hierarchies of Study Design



Comment: Simplistic hierarchies of research design evolved in the 1990s, designating RCTs as "gold standard" and suggesting other study designs are not trustworthy

Adapted from Sackett Evidence-Based Medicine, BMJ 1996

Contemporary Opinions Regarding Study Design

‘The Magic of Randomization versus the Myth of Real-World Evidence’

“[…] because of the potential biases in observational studies, such studies cannot generally be trusted […] the replacement of randomized trials with nonrandomized observational analyses is a false solution to the serious problem of ensuring that patients receive treatments that are both safe and effective.” (Collins, *New Engl J Med* 2020;382:674)

‘Misunderstanding randomized controlled trials’

“We argue that any special status for RCTs is unwarranted. Which method is likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known.” (Deaton & Cartwright, *Soc Sci Med*, 2018;210:2)

Study Design in the Era of Real-World Evidence

Randomized, observational, interventional, and real-world—What's in a name?

John Concato[1] | Peter Stein[2] | Gerald J. Dal Pan[3] | Robert Ball[3] | Jacqueline Corrigan-Curay[1]

In the current era of RWE, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives. In this context, a "randomized trial versus observational study" dichotomy is overly simplistic as short hand for strength of study design to support causal inference. Clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s), as well as an assessment of prognostic determinism for the corresponding cause-effect association.

Pharmacoepidemiol Drug Saf. 2020;29:1514–1517

Comments on 'Big Data'

Origin: term appeared in computer science literature during 1990s, often referring to data too large to be stored in then-conventional storage systems

Contemporary usage: "It's unclear when 'big data' became the buzzword of the day. Or, really, what it means." (Fallik *Health Aff (Millwood)* 2014;33:1111)

Perspective: modern technology has increased quantity and forms of available data as well as the speed to merge and manipulate data, yet integration and analysis of large-scale data has always been integral to epidemiology

Comments on 'Real-World Evidence'

Origin: "real world" is a non-specific modifier; "real-world data" (RWD) and "real-world evidence" (RWE) appeared in medical literature as of the 1970s or earlier, in various contexts

Contemporary usage: RWD and RWE have formal regulatory definitions

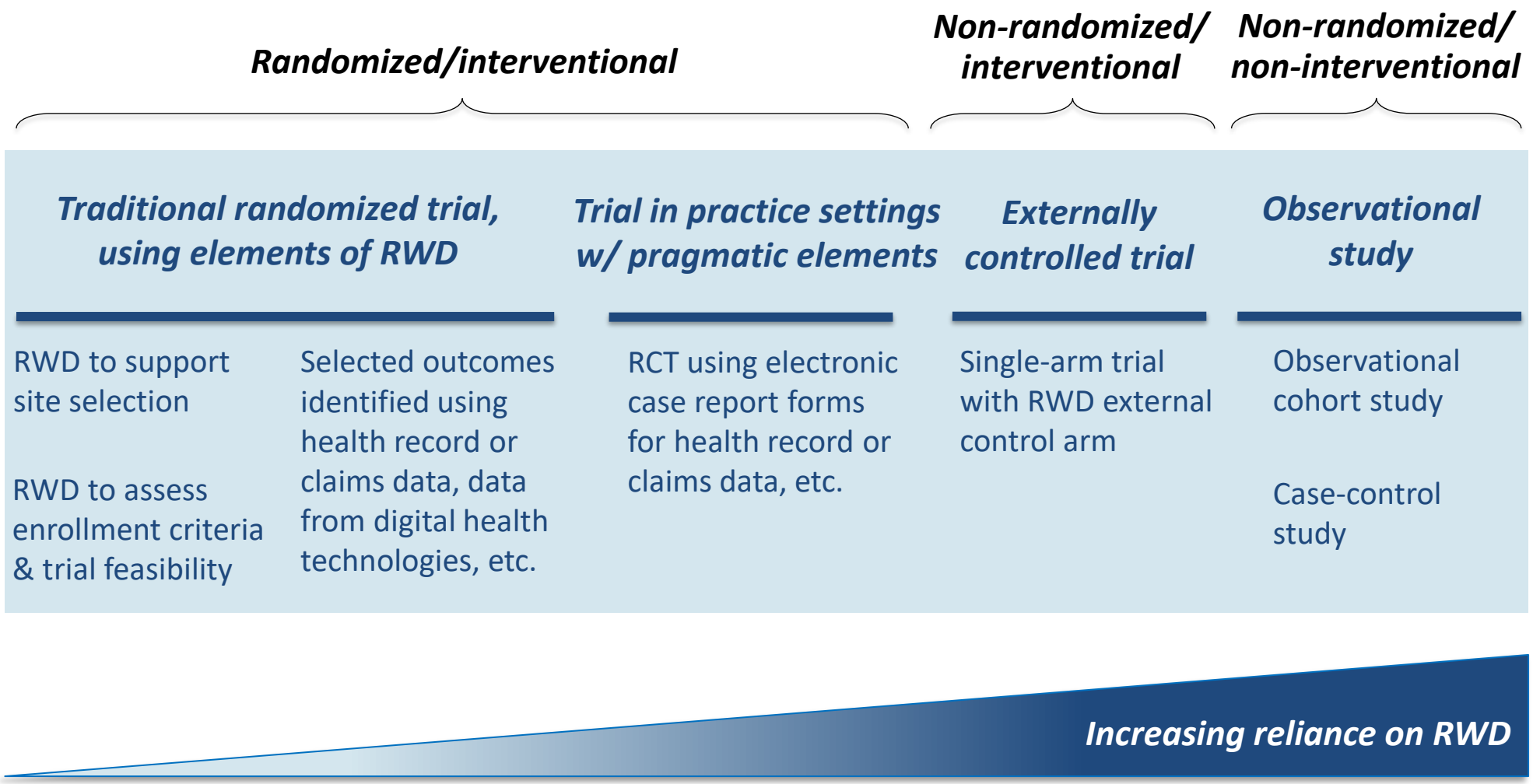
Perspective: older epidemiologic terms were sufficient, but emergence of big data and enactment of 21st Century Cures has led to (sometimes confusing) use of different taxonomies for study design

Example: RWE study ≠ observational study; specific details are needed to classify study design

Contemporary Terms for Study Design

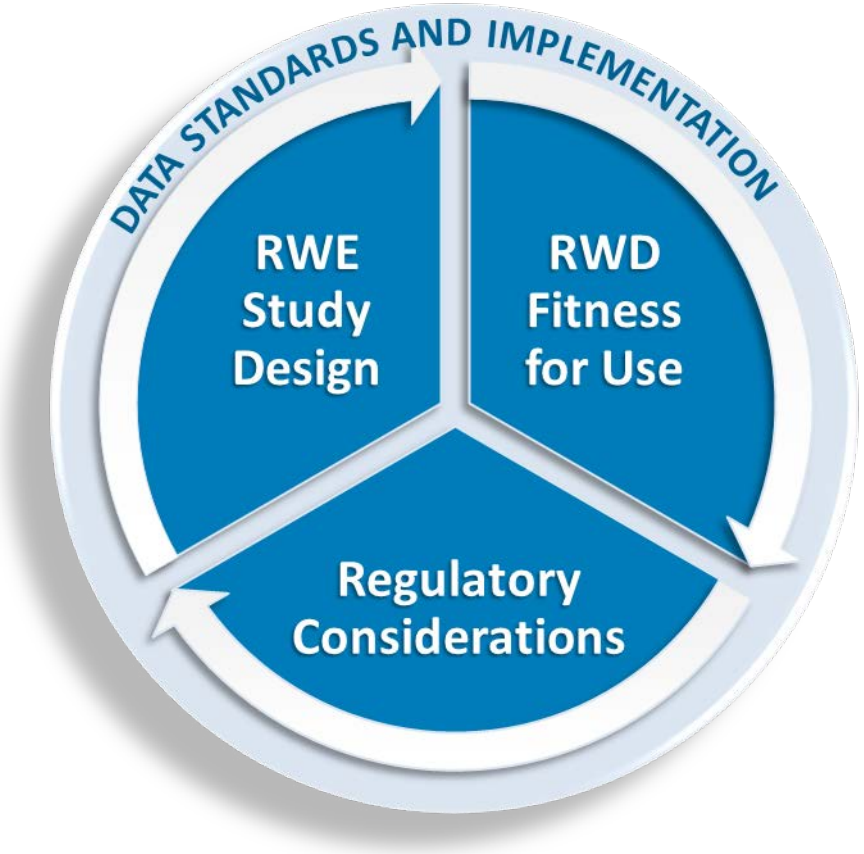
- ***Interventional study*** **(*clinical trial*) – study in which patients are assigned to ≥1 treatment groups, according to a study protocol, to evaluate the effects of a treatment of interest on subsequent health-related outcomes**
  - **e.g., *randomized controlled trials*, *single-arm trials***
- ***Non-interventional study*** **(*observational study*) – study in which patients are not assigned to a study arm according to a protocol, but instead receive the drug of interest during routine medical practice.**
  - **e.g., *observational cohort studies* (patients identified based on drugs received, with subsequent outcomes identified), or *case-control studies* (patients identified based on health outcomes, with antecedent drug use determined)**
- **Combination interventional & non-interventional, and other designs**
  - **e.g., externally controlled trials (clinical trial arm & arm from other data source)**

Overview of Real-World Data and Study Design



CDER-OMP Nov 2021

FDA Approach to Evaluating RWE



Key considerations:

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

RWE Informs Effectiveness When Fit-for-Purpose

DRUG	INDICATION	APPROVED	DATA
Carbaglu *(carglumic acid)*	Treatment of NAGS deficiency	2010	▪ Retrospective, non-random, unblinded **case series of 23 patients compared to historical control group**
Voraxaze *(glucarpidase)*	Treatment of MTX toxicity	2012	▪ Approval based on open-label, **NIH expanded access protocol**
Blincyto *(Blinatumomab)*	Treatment of Acute Lymphoblastic Leukemia	2014	▪ Single-arm trial ▪ Reference group weighted analysis of patient level **data on chart review of 694 patients at EU and US study sites**
Vistogard *(uridine triacetate)*	Overdose of chemotherapy drugs 5-fluorouracil (5-FU)	2015	▪ Two single-arm, open-label expanded access trial of **137 patients compared to case history control**

List not exhaustive

Bold = RWD

RWE Informs Effectiveness (cont'd)

DRUG	INDICATION	APPROVED	DATA
Defitelio *(defibrotide sodium)*	Severe hepatic veno-occlusive disorder	2016	▪ Two prospective clinical trials enrolling 179 patients and **an expanded access study with 351 patients**
Lutathera *(lutetium 177 dotate)*	Gastroenteropancreatic neuroendocrine tumours (GEP-NETs)	2017	▪ Open-label clinical trial ▪ **Analysis of a subset of 360 patients who participated in an investigator sponsored, open-label, single-arm, single institution study of 1214 patients that started as an expanded access program**
Zostavax *(Zoster Vaccine Live)*	Prevention of herpes zoster (shingles) in persons 50 years of age and older	2018	▪ **Prospective, observational cohort study using electronic health records in Kaiser Permanente Northern California (KPNC)** to characterize the duration of protection in persons 50 years of age and older
Ibrance *(palbociclib)*	Men with certain types of advanced or metastatic breast cancer	2019	▪ Data from electronic health records and postmarketing reports of the **real-world use of IBRANCE in male patients**

List not exhaustive

Bold = RWD

New Indication for Prograf Based on RWE


FDA Approves New Use of Transplant Drug Based on Real-World Evidence

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- Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and the drug is used widely in clinical care
- RCTs not done for lung transplant, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with non-interventional 'RWE' study
- Study data and design were evaluated according to FDA standards
- Approval for preventing rejection/death in lung transplant granted 16 Jul 2021

New Indication for Prograf Based on RWE (cont'd)

Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017

Design: non-interventional (observational) treatment arm, compared to historical controls

Review: FDA determined this non-interventional study w/ historical controls to be adequate and well-controlled. Of note, outcomes of organ rejection and death are virtually certain without therapy, and the dramatic effect of treatment helps to preclude bias as explanation of results.

Summary

- **FDA Real-World Evidence Program is advancing as outlined in the agency's 2018 Framework for Real-World Evidence**
- **Older terms for study design in drug development are now joined by newer terms describing the same designs**
- **New and sometimes confusing terminology (e.g., randomized trials can generate RWE) is linked to emergence of "big data" and passage of 21st Century Cures Act; *randomized trials vs. observational studies* is an oversimplified dichotomy**
- **FDA approves drugs using "real-world evidence" in various ways**

Knowledge Check

True or false?

- **Randomized trials are not within the scope of real-world data/real-world evidence? [*false*]**
- **Real-world evidence studies for effectiveness or safety are held to a different (i.e., lower) evidentiary standard than randomized trials? [*false*]**

Additional Information – RWD/RWE Guidance

Recent CDER-CBER guidance on RWD/RWE (in chronological order):

"EHR/claims data" draft guidance: Considerations for selecting fit-for-use real-world data from EHR or medical claims databases to help answer research questions of interest. Sep 2021; https://www.fda.gov/media/152503/download

"Data standards" draft guidance: Recommendations for complying with the Federal Food, Drug, and Cosmetic Act when submitting study data derived from real-world data sources in an applicable regulatory submission. Oct 2021; https://www.fda.gov/media/153341/download

Additional Info – RWD/RWE Guidance (cont'd)

Recent CDER-CBER guidance on RWD/RWE (in chronological order):

"Registry data" draft guidance: Considerations when designing a registry or proposing to use an existing registry to support a regulatory decision. Nov 2021; https://www.fda.gov/media/154449/download

"Regulatory considerations" draft guidance: Expectations for the design and conduct of non-interventional (observational) studies that are not subject to FDA's investigational new drug regulations. Dec 2021; https://www.fda.gov/media/154714/download